Formulations

The present invention relates to novel pharmaceutical formulations of particulate medicaments such as beta-agonists and/or anti-inflammatory steroids in hydrofluoroalkane propellants such as 1,1,1,2-tetrafluoroethane (134a) and/or 1,1,1,2,3,3,3-heptafluoro-n-propane (227) with the carboxyclic acid surfactant compound [(7,7,8,8,8-pentafluorooctyl)oxy]acetic acid, a process for the preparation of said formulations and their use in therapy. The invention also relates to the use of said surfactant in such suspension formulations to enhance the emitted dose, in reducing the variability in the content uniformity of formulations or in providing enhanced Fine Particle Mass (FPM) and / or improved FPM stability.

The use of aerosols to administer medicaments has been known for several decades. Such aerosols generally comprise the medicament, one or more chlorofluorocarbon propellants and either a surfactant or a co-solvent, such as ethanol. Historically the most commonly used aerosol propellants for medicaments have been propellant 11 (CCl_3F) and/or propellant 114 (CF_2ClCF_2Cl) with propellant 12 (CCl_2F_2). However these propellants are now believed to provoke the degradation of stratospheric ozone and there is thus a need to provide aerosol formulations for medicaments which employ so called "ozone-friendly" propellants.

A class of propellants which are believed to have minimal ozone-depleting effects in comparison to conventional chlorofluorocarbons comprise fluorocarbons and hydrogen-containing chlorofluorocarbons, and a number of medicinal aerosol formulations using such propellant systems are disclosed in, for example, EP0372777, WO91/04011, WO91/11173, WO91/11495 and WO91/14422. These applications are all concerned with the preparation of pressurised aerosols for the administration of medicaments and seek to overcome the problems associated with the use of the new class of propellants, in particular the problems of stability associated with the pharmaceutical formulations prepared. The applications all propose the addition of one or more of adjuvants such as alcohols, alkanes, dimethyl ether, surfactants (including fluorinated and non-fluorinated surfactants, carboxylic acids, polyethoxylates etc) and even conventional chlorofluorocarbon propellants in small amounts intended to minimise potential ozone damage.

WO92/00061 discloses non-fluorinated surfactants for use with fluorocarbon propellants.

It is essential that the prescribed dose of aerosol medication delivered from the MDI to the patient consistently meets the specifications claimed by the manufacturer and comply with the requirements of the FDA and other regulatory authorities. That is, every dose dispensed from the can must be the same within close tolerances. Therefore it is important that the formulation be substantially homogenous throughout the canister and the administered dose at the time of actuation of the metering valve and remains substantially the same even after storage. Thus the uniformity of the dose dispensed through the life of the device is vitally important.

In the case of suspension formulations, to control aggregation of fine particles, and thereby influence the dispersability of the suspension it is well established in the art that fluorinated surfactants may be used to stabilise micronised drug suspensions in fluorocarbon propellants such as 134a or 227, see for example US4352789, US5126123, US5376359, US application 09/580008, WO91/11173, WO91/14422, WO92/00062 and WO96/09816.

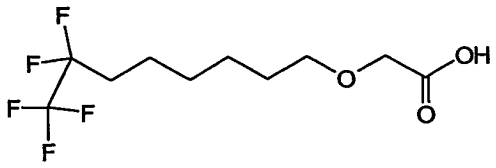
The problem of aggregation of the particulate drug may be manifest as a drop in fine particle mass (FPM) after storage. The FPM is a measure of the dose dispensed which has the potential to reach the therapeutic portion of the lung. Thus a drop in FPM means the therapeutically effective amount of drug available to the patient is reduced which is undesirable and may ultimately be dangerous. This problem is particularly acute when the dose due to be dispensed is low, which is the case for certain potent drugs such as long acting beta agonists.

Furthermore, it is desirable to have a mass median aerodynamic diameter (MMAD) of particles which is within a controlled predetermined range to maximise the therapeutic effect of the dose dispensed. The MMAD has proved difficult to control, in many instances for formulations of the new propellants.

Suspension formulations which are not adequately stabilised result in high levels of drug deposition, for example, on the canister walls or on components of the metered dose inhaler, such as the valve components including the metering chamber, seals or the like. This deposition may not only result in drug loss thereby reducing the total drug content of

the canister available to patient but can also adversely affect the functioning of the device, resulting in the valve sticking, orifices becoming blocked, caking of drug which may work free at a latter point and increase the dose given to the patient in an unpredictable way. Furthermore, expensive modifications to the canister and/or valve may be required to deal with this deposition.

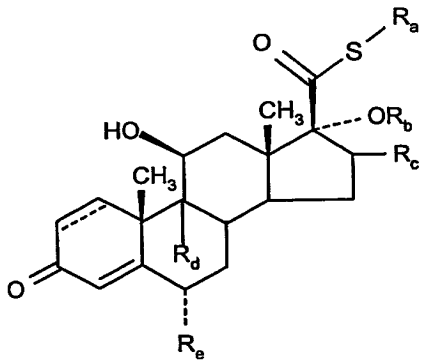
While the use of surfactants, including certain polyoxyethylene surfactants has been suggested, for example in WO95/15151, US 5676931 and WO92/00061, the inventors have now found [(7,7,8,8,8-pentafluorooctyl)oxy]acetic acid which has the formula



has particularly good surfactant properties in 1,1,1,2-tetrafluoroethane and/or 1,1,1,2,3,3,3-heptafluoro-n-propane in comparison to the general class of surfactants, and is particularly useful when employed in pharmaceutical aerosol formulations for administering a particulate medicament of formula (I) and/or of formula (II), the structures of which are given below, to the lungs thereby ameliorating or solving one or more of the above problems.

Thus the invention provides pharmaceutical aerosol formulations comprising:

i) a therapeutic effective amount of particulate medicament selected from a compound of formula (I)



(I)

or a salt, solvate or physiologically functional derivative thereof, wherein

R_a represents C_{1-6} alkyl or C_{1-6} haloalkyl;

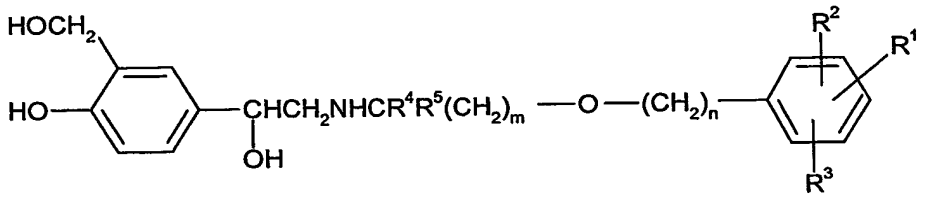
R_b represents -C(=O)-aryl or -C(=O)-heteroaryl;

R_c represents hydrogen, methyl (which may be in either the α or β configuration) or methylene;

R_d and R_e are the same or different and each represents hydrogen or halogen; and

⎓ represents a single or a double bond

and / or a compound of formula (II)



(II)

or a salt, solvate or physiologically functional derivative thereof, wherein:

m is an integer of from 2 to 8;

n is an integer of from 3 to 11;

with the proviso that m + n is 5 to 19;

R^1 is $-XSO_2NR^6R^7$

wherein X is $-(CH_2)_p-$ or C_{2-6} alkenylene;

R^6 and R^7 are independently selected from hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, $C(O)NR^8R^9$, phenyl, and phenyl (C_{1-4}alkyl)-,

or R^6 and R^7, together with the nitrogen to which they are bonded, form a 5-, 6-, or 7-membered nitrogen containing ring,

and R^6 and R^7 are each optionally substituted by one or two groups selected from halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, hydroxy-substituted C_{1-6}alkoxy, $-CO_2R^8$, $-SO_2NR^8R^9$, $-CONR^8R^9$, $-NR^8C(O)R^9$, or a 5-, 6- or 7-membered heterocylic ring;

R^8 and R^9 are independently selected from hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl, and phenyl (C_{1-4}alkyl)-; and

p is an integer of from 0 to 6;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, halo, phenyl, and C_{1-6}haloalkyl; and

R^4 and R^5 are independently selected from hydrogen and C_{1-4}alkyl with the proviso that the total number of carbon atoms in R^4 and R^5 is not more than 4;

(ii) a propellant selected from the group comprising 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heterofluoro-n-propane and mixtures thereof; and

(iii) the surfactant [(7,7,8,8,8-pentafluorooctyl)oxy]acetic acid.

Compounds of formula (I) can be prepared in accordance with procedures described in WO 02/12265 and WO 02/12266. Compounds of formula (II) can be prepared in accordance with procedures described in WO 02/066422. Suitable examples of salts, solvates and physiologically functional derivatives of the compounds of formula (I) and (II) include those described in the patent applications mentioned above.

Advantageously, the surfactant compound of the present invention has good surfactant properties, such as reducing the mean length weighted diameter of suspension formulations, stabilising FPM and/or giving good content uniformity performance, of formulations of the above medicaments in 134a and/or 227 whilst avoiding toxic effects observed for certain perfluorinated surfactant compounds. Usually the best surfactants in 134a and 227 are perfluorinated compounds with a large number of perfluorinated carbon atoms, which unfortunately have a tendency to bioaccumulate. Thus there is an inherent conflict between good surfactant properties and minimising toxic effects. The present invention is advantageous in terms of improving the stability of the aerosol formulation by reducing drug deposition, increasing shelf life and the like.

Whilst not wishing to be bound by theory it is thought that the properties of the surfactant are particularly well matched to those of the medicaments employed in the formulations of the present invention, for example, in respect of their pKa and thereby provide good stabilising effects.

In a first aspect the invention provides a pharmaceutical aerosol formulation wherein the particulate medicament comprises 3-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl) phenyl]ethyl} amino)hexyl]oxy}butyl) benzenesulfonamide or 3-(3-{[7-({(2R)-2-hydroxy-2-[4-hydroxy-3-hydroxymethyl)phenyl]ethyl}amino)heptyl]oxy}propyl) benzenesulfonamide.

In a second aspect the invention provides a pharmaceutical aerosol formulation wherein the particulate medicament comprises 6α, 9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester or 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester.

In a third aspect the present invention provides a pharmaceutical aerosol formulation wherein the particulate medicament comprises 3-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl) phenyl]ethyl} amino)hexyl]oxy}butyl) benzenesulfonamide and (in combination with) 6α, 9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester or 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester.

In a fourth aspect the present invention provides a pharmaceutical aerosol formulation wherein the particulate medicament comprises 3-(3-{[7-({(2R)-2-hydroxy-2-[4-hydroxy-3-hydroxymethyl)phenyl]ethyl}amino)heptyl]oxy}propyl) benzenesulfonamide and (in combination with) 6α, 9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester or 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester.

The specific compounds described in the above embodiments of the present invention above can be in the form of salts, solvates and physiologically functional derivatives thereof. Where the medicament employed is or includes 3-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl) phenyl]ethyl} amino)hexyl]oxy}butyl) benzenesulfonamide, preferably it is employed as the cinnamate salt.

In an alternative aspect the invention also extends to formulations comprising [(7,7,8,8,8-pentafluorooctyl)oxy]acetic acid, a propellant such as 134a and/or 227 and a particulate drug selected from the group comprising:
N-(3,5-dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide,
a compound of formula (I) as disclosed in WO03/024439 (in particular 4-{(1*R*)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol),

a compound of formula (II) as disclosed in WO01/42193 (in particular N-[2-hydroxy-5-[(1*R*)-1-hydroxy-2-[[2-4-[[(2R)-2-hydroxy-2-phenylethyl]amino] phenyl]ethyl]amino]ethyl]phenyl]formamide),
a compound of formula (I) as disclosed in WO03/042160 (in particular N-{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine), and
a compound of formula (I) as disclosed in WO03/042164 and combinations thereof.

The surfactant [(7,7,8,8,8-Pentafluorooctyl)oxy]acetic acid can be prepared by methods as described in WO03/013610.

Use of said surfactant compound for the preparation of formulations according to the present invention results in effective suspension stabilisation at low concentrations relative to the amount of medicament. Thus, the amount of the surfactant employed is desirably in the range of 0.05% to 20% w/w, particularly 0.5% to 10% w/w relative to the medicament.

The particle size of the particulate (e.g. micronised) medicament should be such as to permit inhalation of substantially all of the medicament into the lungs or nasal cavity upon administration of the aerosol formulation and will thus be less than 100 microns, desirably less than 20 microns, and preferably will have a MMAD in the range 1-10 microns, e.g. 1-5 microns.

The final aerosol formulation desirably contains 0.005-10% w/w, preferably 0.005 - 5% w/w, especially 0.01-1.0% w/w, of medicament relative to the total weight of the formulation.

Preferably a single propellant is employed, for example, 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoro-n-propane, especially 1,1,1,2-tetrafluoroethane.

It is desirable that the formulations of the invention contain no components which may provoke the degradation of stratospheric ozone. In particular it is desirable that the formulations are substantially free of chlorofluorocarbons such as CCl_3F, CCl_2F_2 and CF_3CCl_3.

If desired the propellant may additionally contain a volatile adjuvant such as a saturated hydrocarbon, for example, propane, n-butane, isobutane, pentane and isopentane or a dialkyl ether, for example, dimethyl ether. In general, up to 50% w/w of the propellant may comprise a volatile hydrocarbon, for example 1 to 30% w/w. However, formulations which are substantially free of volatile adjuvants are preferred. In certain cases, it may be desirable to include appropriate amounts of water, which can be advantageous in modifying the dielectric properties of the propellant.

Polar adjuvants which may if desired, be incorporated into the formulations according to the present invention include, for example, C_{2-6}aliphatic alcohols and polyols such as ethanol, isopropanol and propylene glycol and mixtures thereof. Preferably ethanol will be employed. In general only small quantities (e.g. 0.05 to 3.0% w/w) of polar adjuvants are required and the use of quantities in excess of 5% w/w may disadvantageously tend to dissolve the medicament. Formulations preferably contain less than 1% w/w, for example, about 0.1% w/w of polar adjuvant. Most preferably the formulations according to the invention are substantially free of polar adjuvant. Polarity may be determined, for example, by the method described in European Patent Application Publication No. 0327777.

In addition to the surfactant, the formulations according to the present invention may optionally contain one or more further ingredients conventionally used in the art of pharmaceutical aerosol formulation. Such optional ingredients include, but are not limited to, taste masking agents, sugars, buffers, antioxidants, water and chemical stabilisers.

A particularly preferred embodiment of the invention provides a pharmaceutical aerosol formulation consisting essentially of one or more particulate medicament(s) of formula (I) and/or formula (II), or other medicament disclosed in this specification or combination thereof, one or more of said propellants and [(7,7,8,8,8-pentafluorooctyl)oxy]acetic acid.

The invention also extends to formulations as described already which "consist of" rather than comprise or consist essentially of said elements.

A further embodiment of the invention is a sealed container capable of withstanding the pressure required to maintain the propellant as a liquid, such as a metered dose inhaler, containing therein one of the aerosol formulation as described above.

The term " metered dose inhaler" or MDI means a unit comprising a can, a secured cap covering the can and a formulation metering valve situated in the cap. MDI system includes a suitable channelling device. Suitable channelling devices comprise for example, a valve actuator and a cylindrical or cone-like passage through which medicament may be delivered from the filled canister via the metering valve to the nose or mouth of a patient such as a mouthpiece actuator.

MDI canisters generally comprise a container capable of withstanding the vapour pressure of the propellant used such as a plastic or plastic-coated glass bottle or preferably a metal can, for example, aluminium or an alloy thereof which may optionally be anodised, lacquer-coated and/or plastic-coated (e.g. incorporated herein by reference WO96/32099 wherein part or all of the internal surfaces are coated with one or more fluorocarbon polymers optionally in combination with one or more non-fluorocarbon polymers), which container is closed with a metering valve. The cap may be secured onto the can via ultrasonic welding, screw fitting or crimping. MDIs taught herein may be prepared by methods of the art (e.g., see Byron, above and WO96/32099). Preferably the canister is fitted with a cap assembly, wherein a drug metering valve is situated in the cap, and said cap is crimped in place.

Advantageously formulations according to the present invention may obviate the need for the additional processing of the canisters and/or component by, for example, coating which ultimately leads to cost saving, especially when manufacturing in bulk.

The metering valves are designed to deliver a metered amount of the formulation per actuation and incorporate a gasket to prevent leakage of propellant through the valve. The gasket may comprise any suitable elastomeric material such as, for example, low density polyethylene, chlorobutyl, black and white butadiene-acrylonitrile rubbers, butyl rubber and neoprene. Suitable valves are commercially available from manufacturers well known in the aerosol industry, for example, from Valois, France (e.g. DF10, DF30, DF60), Bespak plc, UK (e.g. BK300, BK357) and 3M-Neotechnic Ltd, UK (e.g. Spraymiser^{TM}).

The formulations of the invention may be prepared by dispersal of a compound of formula (I) and/or (II) or other medicament as appropriate and the chosen surfactant compound in the selected propellant in an appropriate container, for example, with the aid of sonication

or a high-shear mixer. The process is desirably carried out under controlled humidity conditions.

Alternatively the surfactant compound may be prespiked into an empty canister before the cap and valve are secured in place.

A further aspect of this invention comprises a process for filling the said formulation into MDIs.

Conventional bulk manufacturing methods and machinery well known to those skilled in the art of pharmaceutical aerosol manufacture may be employed for the preparation of large scale batches for the commercial production of filled canisters. Thus, for example, in one bulk manufacturing method a metering valve is crimped onto an aluminium can to form an empty canister. The particulate medicament is added to a charge vessel and liquefied propellant is pressure filled through the charge vessel into a manufacturing vessel, together with liquefied propellant containing the surfactant. The drug suspension is mixed before recirculation to a filling machine and an aliquot of the drug suspension is then filled through the metering valve into the canister.

In an alternative process, an aliquot of the liquefied formulation is added to an open canister under conditions which are sufficiently cold to ensure formulation does not vaporise, and then a metering valve crimped onto the canister.

Typically, in batches prepared for pharmaceutical use, each filled canister is check-weighed, coded with a batch number and packed into a tray for storage before release testing.

Each filled canister is conveniently fitted into a suitable channelling device prior to use to form a metered dose inhaler system for administration of the medicament into the lungs or nasal cavity of a patient.

The chemical and physical stability and the pharmaceutical acceptability of the aerosol formulations according to the invention may be determined by techniques well known to those skilled in the art. Thus, for example, the chemical stability of the components may be determined by HPLC assay, for example, after prolonged storage of the product.

Physical stability data may be gained from other conventional analytical techniques such as, for example, by leak testing, by valve delivery assay (average shot weights per actuation), by dose reproducibility assay (active ingredient per actuation) and spray distribution analysis.

The suspension stability of the aerosol formulations according to the invention may be measured by conventional techniques, for example, by measuring flocculation size distribution by image analysis and / or by measuring particle size distribution by cascade impaction or by the "twin impinger" analytical process. As used herein reference to the "twin impinger" assay means "Determination of the deposition of the emitted dose in pressurised inhalations using apparatus A" as defined in British Pharmacopaeia 1988, pages A204-207, Appendix XVII C. Such techniques enable the "respirable fraction" of the aerosol formulations to be calculated. One method used to calculate the "respirable fraction" is by reference to "fine particle mass" which is the amount of active ingredient collected in the lower impingement chamber per actuation expressed as a percentage of the total amount of active ingredient delivered per actuation using the twin impinger method described above.

Metered dose inhalers are designed to deliver a fixed unit dosage of medicament per actuation or "puff", for example, in the range of 1 to 5000 micrograms of medicament per puff.

In a further or alternative aspect the present invention also provides for a method of treatment or prophylaxis of respiratory disorders which comprises administering to a patient in need thereof a pharmaceutical aerosol formulation according to the present invention.

According to another aspect the present invention provides for the use of a pharmaceutical aerosol formulation according to the present invention for the manufacture of a medicament for administration by inhalation for the treatment of respiratory disorders.

Suitable examples of respiratory disorders include, but are not limited to, asthma, bronchitis, chronic obstructive pulmonary disease (COPD), emphysema and rhinitis. Preferably the respiratory disorder is asthma or COPD, in particular asthma.

Administration of medicament may be indicated for the treatment of mild, moderate, severe acute or chronic symptoms or for prophylactic treatment. It will be appreciated that the precise dose administered will depend on the age and condition of the patient, the particular particulate medicament used and the frequency of administration and will ultimately be at the discretion of the attendant physician. When combinations of medicaments are employed the dose of each component of the combination will in general be that employed for each component when used alone. Typically, administration may be one or more times, for example, from 1 to 8 times per day, giving for example 1, 2, 3 or 4 puffs each time.

An appropriate dosing regime for other medicaments will be known or readily available to persons skilled in the art.

The present invention also provides for the use of the surfactant [(7,7,8,8,8-pentafluorooctyl)oxy]acetic acid to enhance the FPM and / or improve FPM stability of pharmaceutical aerosol formulations comprising of one or more particulate medicament(s) of formula (I) and/or formula (II), or other medicament disclosed in this specification or combination thereof and one or more of said propellants.

The present invention also provides for the use of the surfactant [(7,7,8,8,8-pentafluorooctyl)oxy]acetic acid to reduce the variability in the content uniformity, for example, by reducing the relative standard deviation (RSD) of pharmaceutical aerosol formulations comprising of one or more particulate medicament(s) of formula (I) and/or formula (II), or other medicament disclosed in this specification or combination thereof and one or more of said propellants.

The following non-limiting examples serve to illustrate the invention.

Examples

Example 1

Standard 8 mL MDI cans, coated with a polymer blend of PTFE and polyether sulfone, were pre-spiked with 0.6 mg of [(7,7,8,8,8-pentafluorooctyl)oxy]acetic acid , the valves crimped in place, and a suspension of about 6mg 3-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl) phenyl]ethyl} amino)hexyl]oxy}butyl) benzenesulfonamide (DRUG 1) in

about 12 g P134a was filled through the valve. A corresponding surfactant free control was also prepared (CONTROL 1).

Example 2

Standard 8 mL MDI cans, coated with a polymer blend of PTFE and polyether sulfone, were pre-spiked with 0.6 mg of [(7,7,8,8,8-pentafluorooctyl)oxy]acetic acid, the valves crimped in place, and a suspension of about 6 mg of 6α, 9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester (DRUG 2) in about 12 g of P134a was filled through the valve. A corresponding surfactant free control was also prepared (CONTROL 2).

Example 3

Standard 8 mL MDI cans, coated with a polymer blend of PTFE and polyether sulfone, were pre-spiked with 0.7 mg of [(7,7,8,8,8-pentafluorooctyl)oxy]acetic acid, the valves crimped in place, and a suspension of about 3 mg of 3-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl) phenyl]ethyl} amino)hexyl]oxy}butyl) benzenesulfonamide (DRUG 1) and 4 mg of 6α, 9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester (DRUG 2) in about 12 g of P134a was filled through the valve. A corresponding surfactant free control was also prepared (CONTROL 3).

EXPERIMENTAL DATA

MEAN LENGTH WEIGHTED EQUIVALENT DIAMETER

Mean length weighted equivalent diameter of drug suspensions in propellant P134a.

Mean length weighted equivalent diameter of suspensions was determined by image analysis (Galai CIS-100 image analyser) . It represents the diameter a circle of equivalent area to the object under analysis (weighted by particle diameter in the distribution).

Table 1 shows mean particle size data determined by image analysis using a Galai CIS-100 particle size analyser for sample formulations prepared as described above. In this measurement, particle size is represented as the equivalent diameter of a circle of equal area to the object. The mean is the average of 4 determinations. The particle size

measurement was obtained by transferring the suspensions to a pressurised cell, and video-imaging the sample under shear via a microscope objective.

The equivalent diameter is defined as the diameter of a circle of equal area to the object.

Equivalent Diameter = $\sqrt{\frac{Area}{\pi}}$

The mean equivalent diameter can be weighted by number, length or volume.
e.g. For three particles with equivalent diameters of x, y and z:

$$\text{Mean Number weighted diameter} = \left(\frac{1}{3}\right)x + \left(\frac{1}{3}\right)y + \left(\frac{1}{3}\right)z$$

$$\text{Mean Length weighted diameter} = \left(\frac{x}{x+y+z}\right)x + \left(\frac{y}{x+y+z}\right)y + \left(\frac{z}{x+y+z}\right)z$$

These data show that the surfactant in formulations according to the invention has suspension stabilising properties thereby discouraging flocculation of drug particles. This is seen by the marked reduction in average particle size ("mean length weighted equivalent diameter") when the surfactant is incorporated into the formulation.

TABLE 1

Sample	Mean Length Weighted Equivalent Diameter (μm)
CONTROL 1 (Surfactant-free)	23.8 ± 3.2 μm
Example 1	8.1 ± 0.9 μm
CONTROL 2 (Surfactant-free)	14.8 ± 2.8 μm
Example 2	11.1 ± 1.7 μm

FPM

Table 2 shows data relating to the FPM (the sum of stages 3 to 5) obtained using an Anderson Cascade Impactor stack. Data were obtained at the beginning of use of the device. Controls were prepared corresponding to each of the samples but omitting the surfactant. The analysis of aerosol formulations using such stacks is well known to person skilled in the art. The data is shown as absolute FPM in μg and percentage FPM (in brackets) which expresses absolute FPM as a percentage of the total ex-valve emitted dose. This data is given for an initial timepoint and then after storage for 12 weeks at 40°C and 75% relative humidity.

Table 2 shows samples containing surfactant show an increase in the absolute value of the FPM fraction in most cases. This indicates that a greater proportion of the dose will be available to reach the therapeutic target of in the lung, which is desirable. Furthermore, it can be seen that the FPM for Example 2 is stabilised by the presence of the surfactant.

TABLE 2

	FPM μg (FPM as % of dose emitted ex-valve)	
SAMPLE	**Initial**	**12 Weeks 40°C/75% RH**
CONTROL 1 (Surfactant-free)	6.9 μg (32.9 %)	4.9 μg (22.8%)
Example 1	11.2 μg (43.4 %)	8.8 μg (35.0 %)
CONTROL 2 (Surfactant-free)	7.9 μg (35.5 %)	6.7 μg (31.5%)
Example 2	7.2 μg (33.7 %)	7.2 μg (31.8%)
CONTROL 3 DRUG 1 (Surfactant-free)	3.1 μg (31.0 %)	3.8 μg (38.7 %)
Example 3 DRUG1	4.3 μg (36.5 %)	5.1 μg (46.1 %)
CONTROL 3 DRUG 2 (Surfactant-free)	6.7 μg (30.0 %)	7.1 μg (30.1 %)

Example 3 DRUG 2	8.5 µg (33.2 %)	9.0 µg (36.0 %)

CONTENT UNIFORMITY

The content uniformity of the formulation, the preparation of which is described above, was assessed by dose through use testing. Testing was performed on 10 cans/inhalers at "beginning of use" (BoU) and "end of use" (EoU), after storage for 12 weeks at 40°C and 75% relative humidity. After each inhaler had been primed (4 shots fired to waste), actuations 1 and 2 (BoU) were collected. The next 116 actuations of each inhaler were then fired to waste using an automated method and actuations 119 and 120 (EoU) collected.

The results are quoted in Table 3 as the mean dose for 10 inhalers as a percentage of the nominal dose of the formulation. At the end of use the data is quoted as the variability of the mean dose across the 10 inhalers.

The data shows that the percentage of the target dose is increased in the formulations of the present invention. Furthermore, the variability of the dose dispensed (at the end of use) for the formulations of the invention which contain a surfactant is reduced as can be seen by the reduction in the percentage relative standard deviation.

TABLE 3

SAMPLE	Beginning of Use Dose (% Target)	End of Use Dose Variability (% RSD)
CONTROL 1 (Surfactant-free)	78.8 %	4.0 %
Example 1	89.6 %	2.9 %
CONTROL 2 (Surfactant-free)	85.2 %	7.5 %
Example 2	96.0 %	2.2 %

CONTROL 3 DRUG 1 (Surfactant-free)	80.7 %	5.4 %
Example 3 DRUG 1	88.1%	2.1 %
CONTROL 3 DRUG 2 (Surfactant-free)	95.3 %	4.4 %
Example 3 DRUG 2	97.4 %	2.4 %

Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.